

**IN THE SPECIFICATION:**

**IN THE TITLE:**

**Please amend the title as follows:**

--A METHOD FOR ~~ASSAYING~~TREATING ALZHEIMER'S DISEASE--

**Please insert the following paragraph at page 1, line 4 as follows:**

**--CROSS REFERENCE TO RELATED APPLICATIONS**

The present application is a divisional of Application Serial No. 09/624,965, filed on July 25, 2000, which is a continuation of Application Serial No. 08/757,537, filed on November 27, 1996, now abandoned, which is a continuation of Application Serial No. 08/240,720, filed on September 16, 1994 and issued as U.S. Patent 5,705,401 on January 6, 1998.--

**Please amend the paragraph beginning at page 21, line 10 with the following rewritten paragraph:**

**Characterisation of the putative zinc-binding domain of APP:**

16 µg of the synthesized peptide

GVEFVCCPLAEESDNVDSADAEEEDSDVWWGGAD (SEQ ID NO: 1), representing residues 181-214 of APP<sub>695</sub> (or residues 1891-200), or 16 µg of control peptide, was dissolved in 200 µg of blocking buffer (50 mM Tris-HCl, 1mM MnCl<sub>2</sub> 10 mM β-mercaptoethanol 20% methanol, pH 7.4) and dot-blotted onto PVDF (Immobilon-P, Millipore, Befored, MA) which had been pre-wetted with methanol. The blot was then incubated for 30 mins at 20 °C with 100,000 CPM of <sup>65</sup>Zn<sup>2+</sup> in blocking buffer, in the presence or absence of various concentrations of competing unlabeled Zn<sup>2+</sup> or other divalent cations. After incubation the dot-blot was washed

three times with 200  $\mu$ l of blocking buffer without MnCl<sub>2</sub>, the dot was excised and placed in 10 ml of scintillant and assayed by  $\beta$ -counting.

**Please amend the paragraph beginning at page 29, line 13 with the following rewritten paragraph:**

A putative Zn<sup>2+</sup> binding site was identified by trypsin digestion of APP followed by amino-terminal sequencing of a 6 kDa digestion fragment which bound to Zn<sup>2+</sup> -charged chelating-Sepharose. The fragment sequence was FRGVEFVXXPLA (SEQ ID NO: 2). To further characterize and confirm the Zn<sup>2+</sup> -binding properties of this region of APP, candidate synthetic peptides were studied by dot blot. A synthetic peptide representing residues 181-214 of APP was able to bind Zn<sup>2+</sup> in a saturable and specific manner. The role of the cysteine residues in contributing to this peptide's ability to bind <sup>65</sup>Zn<sup>2+</sup> was determined by studying the ability of the same peptide to bind <sup>65</sup>Zn<sup>2+</sup> where the cysteines in the peptide had been modified by carboxyamidomethylation, and by studying <sup>65</sup>Zn<sup>2+</sup> binding to another synthetic peptide representing residues 189-220 of APP<sub>695</sub>, lacking the cysteine residues at positions 186/187. Both of these peptides were able to bind <sup>65</sup>Zn<sup>2+</sup> significantly above background, but to only approximately 15% of the amount of <sup>65</sup>Zn<sup>2+</sup> binding that occurred using the same quantity of 181-214 peptide (or 181 to 200), indicating that the cysteine residues are obligatory for the zinc-binding properties of this peptide. Similar quantities of other peptides representing other regions of the APP molecule (residues 422-433, 581-601, 645-655) and other control peptides (rennin and Insulin A chain) were unable to bind Zn<sup>2+</sup>, whereas the positive control (Insulin B chain) bound <sup>65</sup>Zn<sup>2+</sup>.

**Please amend the paragraph beginning at page 32, line 16 with the following rewritten paragraph:**

One possible explanation for this finding is that zinc binding to APP could promote heparin binding at a different site on the protein, known to be towards the center of APP, by enhancing the protein's conformational stability. The conformational stabilization caused by zinc may promote the central region of APP to remain open to heparin attachment to residues 98 to 105 of APP<sub>695</sub> (CKRGRKQCKTH)(SEQ ID NO: 3) or residues 318 to 331 of APP<sub>695</sub> (KAKERLEAKHRER)SEQ ID NO: 4, perhaps by a charge effect. When heparin binding occurs in the absence of zinc, the protein may be induced to assume a more globular and protease-resistant conformation. This is zinc binding to APP could stabilize the APP to the extent that heparin binding is prevented from inducing the alteration in APP conformation which increases protease resistivity.